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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HEDGEHOG-RELATED PROPHYLAXIS, THERAPY AND DIAGNOSIS OF GI TRACT CARCINOGENESIS

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(57) **Abstract:** The present invention is based on the key roles played by Hedgehog proteins in the regulation of homeostasis of the adult intestinal epithelium. Ihh is expressed in the adult mammalian colon and provides a lineage-instructive signal and regulates colonic epithelial morphogenesis in a compartmental fashion. Loss of Ihh expression precedes morphological change in colon tumorigenesis, i.e. carcinogenesis, and Ihh was absent in HT-29 colon carcinoma cells. Treatment of cancerous HT-29 cells with exogenous Hedgehog protein restored their differentiation. Ihh thus plays a pivotal role in the maintenance of colonic epithelial homeostasis in the differentiation of the GI tract cells and is essential for the enrolment of these GI tract cells on the Death program thus maintaining homeostasis to avoid or treat carcinogenesis. In addition, in gastric cancer expression of Shh is lost and loss of Shh expression precedes morphological changes in the parietal cells of the stomach. Shh is specifically expressed in fundic glands as well as in gastric heterotopia in the esophagus in Meckel's diverticulum. Shh thus has a unique role as a morphogen in fundic gland homeostasis. The present invention relates to methods in which a source of Hedgehog proteins is used prophylactically or therapeutically to maintain homeostasis of the adult intestinal epithelium. In particular the invention relates methods whereby sources of Hedgehog protein are used to prevent or treat carcinogenesis in adult gastric and colonic tissues. The invention also relates to Hedgehog-based method of diagnosing susceptibility for or the presence of carcinogenesis in the adult GI tract, particularly in gastric and colonic tissues. The invention further provide for compositions to be used in the Hedgehog-based methods of diagnosing, preventing and treating epithelial tumorigenesis in the adult GI tract.

## INTERNATIONAL SEARCH REPORT

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<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 A61K38/00 G01N33/68 C12Q1/68 C12N1/21 A61P35/00 A61K38/17																			
According to International Patent Classification (IPC) or to both national classification and IPC																			
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12Q C07K A61K G01N																			
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched																			
Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE																			
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; padding: 2px;">Category</th> <th style="text-align: left; padding: 2px;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="text-align: left; padding: 2px;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">X</td> <td style="padding: 2px;">WO 99 20298 A (ONTOGENY INC) 29 April 1999 (1999-04-29)</td> <td style="padding: 2px;">1,6, 10-16, 21,28,29 1-29</td> </tr> <tr> <td style="padding: 2px;">Y</td> <td style="padding: 2px;">page 4, line 5 - line 18 page 5, line 5 - line 8 page 8, line 26 - line 28 page 20, line 4 - line 15 page 39, line 21 - line 23 ---</td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">X</td> <td style="padding: 2px;">US 6 271 363 B1 (INGHAM PHILIP W ET AL) 7 August 2001 (2001-08-07) *summary*</td> <td style="padding: 2px;">14-16,21</td> </tr> <tr> <td style="padding: 2px;">Y</td> <td style="padding: 2px;">WO 01 98344 A (BIOGEN INC ;LING LEONA E (US); SANICOLA NADEL MICHELE (US)) 27 December 2001 (2001-12-27) page 102, line 21 - line 23 page 104, line 16 - line 18; example 7 ---</td> <td style="padding: 2px;">1-29</td> </tr> </tbody> </table>					Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	WO 99 20298 A (ONTOGENY INC) 29 April 1999 (1999-04-29)	1,6, 10-16, 21,28,29 1-29	Y	page 4, line 5 - line 18 page 5, line 5 - line 8 page 8, line 26 - line 28 page 20, line 4 - line 15 page 39, line 21 - line 23 ---		X	US 6 271 363 B1 (INGHAM PHILIP W ET AL) 7 August 2001 (2001-08-07) *summary*	14-16,21	Y	WO 01 98344 A (BIOGEN INC ;LING LEONA E (US); SANICOLA NADEL MICHELE (US)) 27 December 2001 (2001-12-27) page 102, line 21 - line 23 page 104, line 16 - line 18; example 7 ---	1-29
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<input type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.																	
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the International filing date *L* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the International filing date but later than the priority date claimed																			
Date of the actual completion of the International search  2 September 2003		Date of mailing of the International search report  09/09/2003																	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  Bayrak, S																	

## INTERNATIONAL SEARCH REPORT

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### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 1-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: 1-24 all partially because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-24 all partially

The claims 1-24 lack clarity because the terms "source" and "suffering from deficiency", or "a deficiency of a hedgehog protein" are unclear and leave the reader in doubt as to the meaning of the technical feature to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). This lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely the use of Hedgehog protein in relation to the therapeutic applications specified in claims 2-5, 8-9, 17-20, 23-24, i.e. carcinogenesis in the GI tract, gastric or colonic cancer, colonic adenomatous polyps, GI tract tumorigenesis, gastro intestinal tract carcinoma, invasive adenocarcinom, small intestinal adenomas, small intestinal cancer, and desmoid tumors.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

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